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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,654	06/13/2001	Leanna M. Levine	2842/3	7335

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	10

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/880,654	LEVINE ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Amendment filed May 21, 2003 (Paper No. 8) in response to the Office Action of November 19, 2002 is acknowledged and has been entered. Claims 1-11 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Sequence listing

The Office acknowledges the receipt of the new sequence listing and the computer readable sequence listing.

Drawings

The office acknowledges the receipt of the new drawings which have been accepted by the draftperson.

Claim Objections

The objection to claims 4, 6, 8, 9 and 10 **is withdrawn** in view of applicant's amendments to the claims, eliminating abbreviations from the claims which have not been previously defined in the claims.

Claim Rejections - 35 USC § 112

The rejection of claim 10 **is maintained**. The claim recites the limitation "Abu" in the claim, according to the abbreviations allowed see MPEP 2422 the abbreviation Abu is 2-Aminobuteric acid. There is insufficient antecedent basis for this limitation in the claim since

claim 3 does not recite 2-aminobuteric acid as one of the enumerated groups. Amending the claim so it is depends from claim 2 would obviate this rejection as Abu is an aminoalkylcarboxylic acid. Applicant's arguments have been fully considered but are not persuasive. Claim 3 as written in limited to the compounds cited of which 2-aminobuteric acid is not one of the compounds listed, therefore the rejection of claim 10 is maintained for not having sufficient antecedent basis to depend on claim 3.

The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention **is withdrawn** in view of applicants amendment to the claim correcting the Sequence error in the claim.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention **is withdrawn** in view of applicants amendment to the claim correcting the Sequence error in the claim.

Claim Rejections - 35 USC § 102

The rejection of claims 1-5, 7, 8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Heath et al. (U.S. Pat. No. 5,235,039) **is withdrawn** in view of applicant's

arguments that the assay measurement only measures total fluorescence and not fluorescent polarization.

Claim Rejections - 35 USC § 103

The rejection of claims 1-11 under 35 U.S.C. 103(a) as being obvious over Heath et al. (U.S. Pat. No. 5,235,039) in view of Welch et al. (PNAS 1991) or Blakeslee et al. (Journal of Immunological Methods, 1976) **is withdrawn**. Applicant's arguments, see Paper No. 8, filed May 21, 2003, with respect to the rejection(s)of claim(s) 1-11 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made below.

New Rejection:

Claim Rejections - 35 USC § 112

Claims 1 and 11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite in that they do not set forth clearly the method steps to carry out "a method of determining the activity of a protease" or " a method of identifying a compound which inhibit a protease" because the nature and the endpoint(s) of claimed methods are ambiguous and unclear. There is an absence or lack of clarity as to critical or resolutions steps or endpoints which reads back on the preamble of the claimed methods. Correction is required.

Claim Rejections - 35 USC § 103

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being obvious over Heath et al. (U.S. Pat. No. 5,235,039, IDS), Bromberg (U.S. Pat. No. 4,203,670) and Maeda (Analytical Biochemistry 1979, IDS) in view of Welch et al. (PNAS 1991, IDS) or Blakeslee et al. (Journal of Immunological Methods, 1976).

The instant invention is drawn to a method of determining the activity of a compound, the compound contains a fluorescent group on one side of an amino acid sequence and a binding group at the opposite end of the amino acid sequence. The compound may or may not contain spacer molecules between the fluorescent group and the amino acid or between the binding group and the amino acid. The instant invention is also directed at identifying compounds that inhibit the activity of a protease. The method comprises steps such as incubating the mixture of protease and substrate and measuring fluorescence polarization of the mixture. When measuring the activity of an inhibitor the inhibitor is added into the mixture as well.

Heath et al. teach a method for rapidly measuring the amount of a hydrolytic enzyme generated or released by a proenzyme in multiple samples wherein the substrate for said enzyme comprises recognition sites on both sides of the cleavage site (see column 11, lines 6-11). The reference additionally teaches an assay method for determining inhibitory activity of test compounds which comprises the steps (see column 11, lines 45 to column 12, line 5): a) incubating in the presence of a test compound a protease and a substrate for said protease wherein said substrate is bonded on one side of the cleavage site with a resin-binding compound and on the opposite side with a reporter molecule; b) transferring the incubation solutions from each well of the multiple-well plate to a second multiple well plate wherein the wells have an

upper and lower chamber separated by a porous membrane, wherein each upper chamber of said wells contains a solution or suspension of resin beads capable of irreversible binding to said resin-binding compound bonded to the substrate and wherein the size of said resin beads precludes passage of the bound substrate, or the hydrolyzed portion thereof bonded to the resin, through said membrane; c) filtering and washing each of said two-chambered wells; and d) measuring the emission in each well of said second plate. It will be recognized by those in the art that the conditions of incubation i.e. time, temperature and pH will vary somewhat depending upon the particular protease-substrate reaction. Typically, standard buffers are employed in the incubations which are in general carried out at mild temperatures of about room temperature to about 40°C. In transferring the incubation solutions to the wells in the second multiple well plate the incubation mixture can be diluted with a suitable buffer to provide a desirable concentration. The preferred resin-binding compound of the invention is biotin. A preferred reporter compound is a fluorescence marking compound such as that formed with the substrate and fluorescein isothiocyanate. Preferred resin beads are polystyrene beads coated with avidin which are commercially available. The reference additionally teaches an assay method for determining inhibitory activity of test compounds which comprises the steps (see column 11, lines 45 to column 12, line 5). The reference teaches a compound that comprises bonding a resin binding compound, such as biotin to one side of a scissile bond of the substrate and a reporter molecule such as a fluorescence marker on the opposite side of the scissile bond (see example 1, column 17). The reference discloses the compound according to Formula 1 in the following way. Z= biotin, m=1, W=Gly, X= 9 amino acids, n=0, W=glycine, 4-aminobutyric acid, 5-aminopentanoic acid, 6-aminocaproic acid or 7-aminoheptanoic acid, Y= FITC (fluorescein

isothiocyanate). Example 1 teaches the compound, biotin-Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys-FITC. The reference utilizes a Pandex Model 784 Screen Machine to measure the fluorescence emitted from the cleaved molecule (see column 12, lines 17-18), the fluorescent compound is detected with an excitation wavelength of 485 nm and an emission wave length of 535 nm (Column 9, lines 21-25), the reference measures tot total fluorescence emitting from the sample but does not distinguish between vertical and horizontal emission. The method required the additional step of separating the cleaved compound from the bound/immobilized compound before measuring the total fluorescence. The reference does not teach a method using the compound biotin-γ-Abu-Gly-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gly-Lys-DTAF. The reference does not teach herpes virus protease cleavage sites.

Bromberg teaches an apparatus for the measurement of polarized light which has passed though an emission filter. The set up requires an excitation wavelength and an emission wavelength filter, the use of the apparatus allows for measurements of extremely small polarization of low-level fluorescence. This increases the ability to measure the change in fluorescence in a sample. The reference teaches the use of the polarization disk for the measurement of the vertical and horizontal light transmission. The reference does not teach measuring the activity of a protease.

Maeda et al. teaches the use of fluorescence polarization for the ability to measure the activity of a protease in solution using substrates, which have been labeled with a fluorochrome. The method offers two advantages over other methods, simplicity and high sensitivity. The present procedure does not require any process such as separation, precipitation, centrifugation or further reactions (see page 225, last paragraph). The data are usually obtained from the

reaction mixture in the cuvette. The reference does not teach a substrate comprising an anchor molecule.

Welch et al. teaches substrates for herpes virus protease, the reference does not teach attaching a flourophore on one end of the peptide sequence and a binding agent at the other end of the peptide sequence.

Blakeslee et al. teaches the conjugation of DTAF to an antibody. The reference teaches that DTAF and FITC have nearly identical properties. However, DTAF is superior to FITV in regards to cost, purity and stability. The reference does not teach using DTAF in a protease substrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize known substrates for the detection of protease activity and apply the fluorescence polarization technique to increase the readable signal produced from the substrate as taught by Maeda et al. or Bromberg. It would have been obvious to one of ordinary skill in the art at the time the invention was made utilize the substrate construction as taught by Heath et al. and apply them to the peptide substrates taught by Welch et al. One would have been motivated to do this in order to develop a one step assay for herpes virus proteases in order to have an easy screening assay. Optimizing experimental conditions, including the addition of spaces between the amino acid and the binding group or fluorescing group, choosing the fluorescing group so that it minimizes quenching and optimizes signal output, falls within the skills of an ordinary artisan. Blakeslee et al. teaches that DTAF and FITC have identical properties, however, because of the lower cost involved with DTAF one having ordinary skill in the art would have been motivated to substitute DTAF for FITC in the substrate taught by Heath et al. Therefore, the

instant invention is obvious over Heath et al., Maeda et al. and Bromberg in view of Welch et al. or Blakeslee et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 8/8/03